REMARKS/ARGUMENTS

1. Claim Amendments

In the amended set of claims, the expression "*HIV vaccine composition*" has been replaced with "*HIV immunogenic composition*". Support for this modification is found throughout the specification (see for example, page 6, lines 19-20 and lines 31-32; page 7, lines 1-4; page 20, lines 14-15 and examples 3, 4 and 7).

In addition, the amended claim 35 specifies that the stabilized Tat antigen is an isolated Tat antigen, since the specification clearly refers to a Tat antigen which is in an isolated form (see for example page 19, line 28 to page 20, line 9 and example 1).

Claims 36, 44, 45, 46, 47, 49, 50, 53 have been amended to overcome the clarity objections as regards these claims.

New claims 67 to 79 were added to incorporate the narrower ranges which were defined in claims 46, 47, 49, 50 and 53 and the subject matter of claim 54.

Claims 54 and 58 have been cancelled.

The new set of claims is supported by the specification and the claims as originally filed. No new matter has been added.

2. Response to the rejections

The aim of the present invention is to provide a composition comprising a Tat antigen which is more immunogenic than the compositions comprising a Tat antigen of the prior art.

The invention provides a stabilized Tat antigen which is more immunogenic than the Tat antigens of the prior art. The stabilized Tat antigen according to the invention consists of: a complex Tat/non-metal ligand of Tat, a modified Tat wherein one or more cysteines are modified with a hydrophobic group and/or substituted with a hydrophobic amino acid, or a complex between said modified Tat and a non-metal ligand of Tat.

2.1 35 USC § 112 first paragraph rejection as regards claims 35-58

The claims which were directed to a HIV vaccine composition were rejected for lacking enablement. This rejection is obviated by amendment, since the new claims are directed to a HIV immunogenic composition.

It is worth noting that in the context of HIV, the vaccine is not a preventive vaccine only as mentioned page 4 of the Office communication but a preventive or curative vaccine as explained below.

In addition, examples showing vaccination with a multi-clade immunogen and challenge with HIV resulting in a complete protection or prevention of HIV infection as requested page 5 of the Office action are not realistic in the context of HIV infection. Complete protection or prevention of HIV infection by vaccination is not realistic.

In fact, the best HIV vaccine is expected to achieve the persistence of a low HIV virus load in the vaccinated subjects. Such HIV vaccine would prevent or limit the development of AIDS in the vaccinated subjects.

Therefore, the transcriptional transactivator (Tat) of HIV is considered as an attractive candidate for the preparation of a therapeutic or preventive vaccine against AIDS since non-progression in infected individuals is correlated to the presence of high anti-Tat antibody titers and of Tat-specific cytotoxic T cells (see page 1, lines 27-34 of the specification of the present application, which refers to Zagury *et al.*, J. Hum. Virol., 1998, 1, 282-292; Re *et al.*, J. Clin. Virol., 2001, 21, 81-9; Van Baalen *et al.*, J. Gen. Virol., 1997, 78, 1913-1918).

The correlation of these *in vivo* observations to viral replication and spreading was provided by *in vitro* studies showing that anti-Tat antibodies inhibit HIV replication (Steinaa *et al.*, Arch. Virol., 1994, 139, 263-271; *Annex 1*).

In addition, it was demonstrated that Tat-specific cytotoxic T lymphocytes cells are significantly involved in controlling HIV virus replication during the acute phase of infection (Allen *et al.*, Nature, 2000, 407, 313-314, *Annex 2*).

Therefore, it is considered that the induction of high anti-Tat antibody titers and of Tat-specific cytotoxic T lymphocytes correlates with human protection against AIDS.

Furthermore, several Tat candidate vaccines were prepared and shown to protect monkeys against a HIV/SIV viral challenge in preclinical studies. These Tat candidate

vaccines include nonmodified biologically active Tat (see page 4, lines 9-12 of the specification of the present application, which refers to Cafaro *et al.*, Nat. Med., 1999, 5, 643-650) and Tat toxoid, the cysteines of which are blocked with acetamidomethyl groups (inactivated Tat; see page 5, lines 31-35, which refers to Pauza *et al.*, Proc. Natl. Acad. Sci. USA, 2000, 97, 3515-3519).

The *in vivo* observations showing a correlation between Tat-specific humoral and cellular immune responses and the protection against AIDS in non-progressors, combined with the preclinical studies in monkeys showing a protective effect of several Tat vaccines against HIV infection, are thus sufficient to reasonably predict that an immunogenic Tat antigen able to induce high anti-Tat antibody titers and Tat-specific cytotoxic T cells might help to prevent AIDS in HIV infected humans.

However, given the unpredictability of the art vis-à-vis HIV vaccine development, the claims have been limited to a HIV immunogenic composition.

The invention provides a stabilized Tat antigen which is more immunogenic than the Tat antigens of the prior art (see page 7, lines 1 to 6; page 20, lines 11-28).

The specification discloses how to make a stabilized Tat antigen and provides an assay to test that a Tat antigen is stabilized (see for example page 19, line 28 to page 20, line 9 and examples 1 and 6).

The specification demonstrates that stabilized Tat derivatives induce anti-Tat antibody titers in animals, which are at least 10 times higher (factor of 10 to 35) than those obtained by immunization with nonmodified Tat or the Tat toxoid (examples 3, 4 and 7; figures 4, 9, 12, 13, 16 and 17).

The specification shows that the antigenic specificity of the anti-Tat antibodies produced by immunization with the stabilized Tat antigen is similar to that of the anti-Tat antibodies produced by immunization with unmodified Tat (example 3 and figure 5).

The specification demonstrates that stabilized Tat derivatives induce both a humoral and cellular response; the comparative studies show that, under the same conditions, unmodified Tat induces a weak humoral response (example 4 and figure 14).

The specification demonstrates that compared to non-modified Tat that is capable of transactivating the HIV LTR, the stabilized Tat derivatives have a reduced transactivating activity (example 5 and figure 15).

The experimental data presented in the present application were published in Vaccine (2008, 26, 2615-626; *Annex 3*).

The examples of the application showing that the stabilized Tat antigen is highly immunogenic were confirmed by further studies from the inventors.

These studies in cynomolgus macaque (Turban *et al.*, manuscript accepted for publication in Vaccine; *Annex 4*), the animal model that is used for HIV vaccine preclinical studies, show that the stabilized Tat derivatives according to the invention raise a potent and long lasting humoral and cellular immune response.

The anti-Tat antibodies appear after only one immunization and their titers remain elevated up to eight weeks after the last immunization. A similar behaviour was found for the cellular immune response. Furthermore, approximatively 50 % of the IFN-γ secreting Tat-specific T cells are CD8 lymphocytes. The macaque sera neutralize the transactivating activity of Tat.

Whether the strong anti-Tat immune response that is raised by the stabilized Tat derivatives according to the invention can protect non-human primates against a viral challenge is currently under investigation.

Therefore it is considered that the claimed HIV immunogenic composition could be practiced without undue experimentation since the above state of the prior art analysis demonstrates the potency of Tat as a vaccine against AIDS, based on (i) *in vivo* observations showing a correlation between Tat-specific humoral and cellular immune responses and the protection against AIDS in non-progressors, and on (ii) preclinical studies in monkeys showing a protective effect of several Tat vaccines against HIV infection. In addition, the specification provides considerable direction and guidance on how to practice the claimed HIV immunogenic composition as well as working examples. The experimental data in mice, provided in the specification showing the immunogenicity of the claimed stabilized Tat antigen were confirmed by data in

cynomolgus macaque (*Annex 4*), the animal model that is used for HIV vaccine preclinical studies.

Withdrawal of the rejection is thus respectfully requested.

2.2 35 USC § 112 second paragraph rejection as regards claims 36, 44, 45, 46, 49, 50, 53, 54 and 58

The objection is obviated by the above mentioned amendments to the claims. Withdrawal of the rejection is therefore respectfully requested.

2.3 35 USC § 102 rejection as regards claims 35, 36, 44 and 54 in view of Marasco *et al.*

Claims 35, 36, 44 and 54 were rejected as being anticipated by Marasco *et al.*

However, Marasco *et al.* does not disclose an HIV immunogenic composition comprising at least one isolated stabilized Tat antigen resistant to proteolytic degradation, said isolated stabilized Tat antigen consisting of an isolated Tat/ligand complex, wherein the ligand is a non-metal ligand of Tat, for example a protein, lipid, carbohydrate, nucleotide, glycolipid or glycoprotein.

The HIV Tat protein is a transcription factor that is essential to viral replication and may also be involved in AIDS pathogenesis.

Therefore the Tat protein is a target for anti-HIV therapy.

Marasco *et al.* relates to intrabody gene therapy for the treatment of HIV infection and AIDS using the Tat protein as a target (see abstract).

The aim of Marasco *et al.* is to introduce anti-HIV Tat intrabody genes into CD4+ T cells to block Tat and thus inhibit HIV replication in these HIV susceptible cells *in vivo*.

Marasco *et al.* relates to anti-HIV therapy (inhibition of HIV infection/replication) which is different from anti-HIV vaccine (induction of a protective immune response against HIV infection and AIDS). Marasco *et al.* does not disclose any HIV antigen, immunogen or immunogenic composition. Marasco et al. simply applied to gene therapy, the experiments made by Steinaa et al., which previously showed that anti-Tat antibodies inhibit HIV replication (Steinaa *et al.*, Arch. Virol., 1994, 139, 263-271; *Annex 1*).

Marasco *et al.* discloses:

- stably transfected CD4+ T cells expressing anti-Tat sFv intrabody which are infected by HIV-1_{IIIB} encoding and subsequently expressing Tat, and
- a recombinant retroviral vector encoding a humanized anti-HIV Tat sFv intrabody for gene therapy of HIV infection and AIDS (figure 3).

Therefore, Marasco *et al.* does not disclose an HIV immunogenic composition comprising at least one isolated stabilized Tat antigen resistant to proteolytic degradation, said isolated stabilized Tat antigen consisting of an isolated Tat/ligand complex.

The Examiner argues that the anti-Tat intrabodies which are produced in the stably transfected cells that are infected by HIV, as disclosed by Marasco *et al.*, inherently protect Tat from proteolytic degradation.

However, this is not necessarily true for the following reasons. The specification of the present application mentions clearly that the core region (central domain; positions 38 to 48 of Tat) of the stabilized Tat antigen according to the invention is protected from proteolytic degradation (see the definition page 9, lines 10 to 20 and the example 6). Therefore, the anti-Tat intrabodies of Marusco *et al.* which are directed to the N-terminal region (positions 1 to 20) or to exon 2 (C-terminal region: positions 73 to the C-terminal end) do not mask the core region of Tat and therefore are not capable to protect this region from proteolytic degradation.

Withdrawal of the rejection is therefore respectfully requested.

2.4 35 USC § 103 (a) rejection as regards claim 35, 36, 37, 44 and 54 over Marasco *et al.*, in further view of Sanchez *et al.*

Marasco *et al.* relates to anti-HIV therapy (inhibition of HIV infection/replication) which is different from anti-HIV vaccination (induction of a protective immune response against HIV infection).

The aim of Marasco *et al.* is to introduce anti-HIV Tat intrabody genes into CD4+ T cells to block Tat and thus inhibit HIV replication in these HIV susceptible cells *in vivo*.

Marasco *et al.* teaches that the binding of some anti-Tat sFv intrabodies to Tat inhibits HIV replication in stably transfected CD4+ T cells expressing anti-Tat sFv intrabody which are infected by HIV-1_{IIIB}.

Marasco *et al.* disclose a recombinant retroviral vector encoding a humanized anti-HIV Tat sFv intrabody for gene therapy of HIV infection and AIDS

Marasco *et al.* does not disclose or suggest an HIV immunogenic composition comprising a Tat antigen; moreover it does not suggest an HIV immunogenic composition comprising a stabilized Tat antigen resistant to proteolytic degradation, said stabilized Tat antigen consisting of an isolated Tat/ligand complex.

Sanchez *et al.* relates to microencapsulated vaccines. Sanchez *et al.* deals with the problem of stabilizing proteins in particular antigenic proteins like tetanus toxoid (TT) inside PLGA microspheres (see abstract and page 256, first column, beginning of first and second paragraph).

Sanchez *et al.* teaches that polysaccharides (dextran and heparin) are efficient protein stabilizing excipients in microspheres as demonstrated by the percentage of antigenically active TT that is released from microspheres.

In addition, contrary to what is stated in page 11 of the Office communication, Sanchez *et al.*, does not teach to use heparin as a stabilizer of protein vaccines since use of heparin compared favorably to several other materials known to stabilize antigenic proteins. The comparative assays presented by Sanchez, clearly show that the best stabilizer for antigenic proteins which are encapsulated in microspheres is dextran. This is confirmed by the immunogenicity studies (Table 4 and 5) that are performed using dextran as a stabilizer for microencapsulated TT.

The protein stabilizing excipients of Sanchez do not protect proteins from proteolytic cleavage. They protect proteins from thermal and chemical stresses (lyophilisation, solvent extraction).

Furthermore and importantly, the TT stabilizing excipients of Sanchez (dextran, heparin) are not TT ligands.

Sanchez *et al.* do not teach polysulfated polysaccharides.

Furthermore, Tables 4 and 5 show that the antigen stabilizer alone does not have any effect on the immunogenicity of the encapsulated antigen. An enhanced antibody production requires the co-administration of the encapsulated antigen in microspheres containing the stabilizer and of alum-adsorbed antigen.

Therefore, Sanchez, like Marasco, does not teach an immunogenic composition comprising an isolated stabilized antigen resistant to proteolytic degradation, said stabilized antigen consisting of an antigenic protein/ligand complex as required in the present invention.

Thus these documents in combination do not disclose all the elements of the invention and cannot render it obvious.

Moreover, there cannot be any suggestion to combine the teaching of these two references to arrive at the invention because of the missing elements.

However, assuming *arguendo* that these documents disclosed each element of the invention, they provided no reasonable expectation of success for the present invention.

Even if the skilled artisan had combined the teaching of Marasco with the teaching of Sanchez for making an HIV immunogenic composition, he would have prepared a composition comprising encapsulated Tat in microspheres containing dextran and alum.

The skilled artisan would have used the microspheres in combination with alum since Sanchez *et al.* teaches that alum is essential to improve the immunogenicity of the antigenic protein (see page 265, first column, end of first paragraph).

The skilled artisan would have used dextran which is not a ligand of Tat.

However, the skilled artisan would not have used the antigenic protein without microspheres since Sanchez *et al.* teaches that the microspheres are essential to achieve high and long lasting titers of neutralizing antibodies.

Even, if the skilled artisan had used a not encapsulated antigenic protein, he would not have used a stabilizer since the stability problems disclosed by Sanchez *et al.* are due to the microspheres and specific to microspheres (microencapsulation techniques, microenvironment created inside PLGA microspheres during polymer degradation, as specified page 256, first column, middle of second paragraph).

Nothing in Marasco or Sanchez suggest an HIV immunogenic composition comprising an isolated stabilized Tat antigen consisting of an isolated Tat/ligand complex.

Accordingly, this rejection cannot be sustained because the cited art does not disclose all the elements of the invention, or suggest or provide a reasonable expectation of success for the present invention.

Furthermore, it is worth noting that in further studies (*Annex 5*), the inventors have shown that the enhanced immunogenicity which is observed when Tat is combined with its heparin ligand to form Tat/heparin complexes is not observed for other antigenic proteins (Vpr, Nef), whether they are heparin ligands (Nef) or not (Vpr). These data indicate that the claimed Tat antigen produces an unexpected effect.

2.5 35 USC § 103 rejection as regards claim 55-57 over Marasco *et al.*, in further view of Lindblad (2004).

Claims 55-57 were rejected under 35 USC § 103 (a) as being unpatentable over Marasco *et al.*, in view of Sanchez *et al.,* and further in view of Lindblad (2004). This rejection is not sustainable over the combination of Marasco and Sanchez for the reasons discussed above. Lindblad was cited as disclosing aluminium adjuvants. However, Lindblad does not suggest the elements missing from the two primary references, such as an HIV immunogenic composition comprising an isolated stabilized Tat antigen consisting of an isolated Tat/ligand complex. Accordingly, this rejection cannot be sustained.

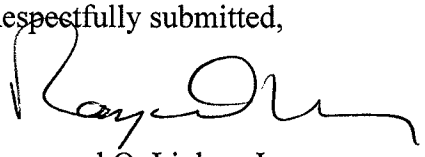
Conclusion

In view of the claim amendments and the foregoing comments and accompanying evidence, it is submitted that all outstanding issues have been overcome and the claims of this application are in condition for immediate allowance. Favorable reconsideration by the Examiner and formal notification of the allowability of the claims are solicited.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR §

1.136(a), and any fee required therefor (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,



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